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PCT

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<p>(54) Title: MEDICAMENTS FOR TREATMENT OF MIGRAINE, EPILEPSY AND FEEDING DISORDERS</p> <p>(57) Abstract</p> <p>A novel method of medical treatment, in particular the treatment and prevention of epilepsy and migraine.</p>		

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MEDICAMENTS FOR TREATMENT OF MIGRAINE, EPILEPSY AND FEEDING DISORDERS

The present invention relates to a novel method of medical treatment, in particular the treatment and prevention of epilepsy and migraine.

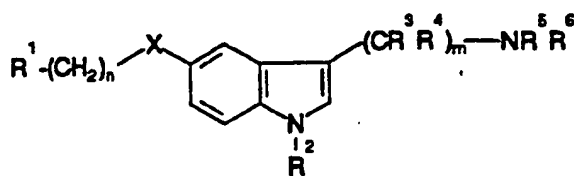
5 Compounds which have activity as 5HT_{2C} receptor antagonists and activity at the rat fundus serotonin receptor are known in the art. Examples of such compounds are disclosed in WO 93/18028 and WO 92/05170.

Rat fundus serotonin receptors are presently known as 5HT_{2B} receptors. It has now been found that these 5HT_{2B} receptors are located in regions of the brain, for
 10 example in the hippocampus, habenula and hypothalamus regions. It is expected, as a consequence, that compounds which exhibit 5HT_{2B} receptor modulating activity will be of use in the treatment of certain CNS disorders, in particular epilepsy, migraine and feeding disorders. It has also been found that these 5HT_{2B} receptors are located in the gastrointestinal tract. Compounds which exhibit 5HT_{2B} receptor modulating activity are
 15 therefore also expected to be of use in the treatment of GI disorders such as irritable bowel syndrome (IBS).

The present invention therefore provides, in a first aspect, the use of a 5HT_{2B} receptor modulator in the treatment of epilepsy, migraine and feeding disorders. It will be appreciated by those skilled in the art that the term '5HT_{2B} receptor modulator' refers to a
 20 compound which acts as an agonist or antagonist at the 5HT_{2B} receptor.

In particular, for the treatment or prophylaxis of epilepsy and feeding disorders such as anorexia nervosa, the 5HT_{2B} receptor modulator should preferably be a 5HT_{2B} receptor agonist. Preferred 5HT_{2B} receptor agonists include compounds of formula (I) and pharmaceutically acceptable salts thereof:

25



(I)

30 in which

R¹ is an optionally substituted phenyl, thienyl or furyl ring;

R² is hydrogen or C₁₋₆ alkyl;

R³ and R⁴ are independently hydrogen or C₁₋₆ alkyl;

R⁵ and R⁶ are independently hydrogen or C₁₋₆ alkyl;

X is O, S or NH; and

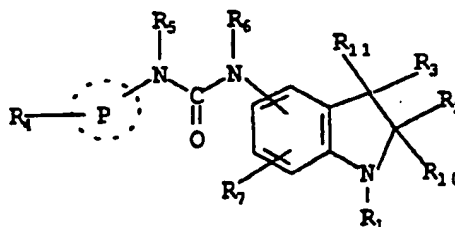
n and m are independently 1 or 2.

A particularly preferred 5HT_{2B} receptor agonist of formula (I) is 1-(5-(2-thienylmethoxy)-1H-indol-3-yl)propan-2-amine.

- 5 For the treatment or prophylaxis of migraine and IBS the 5HT_{2B} receptor modulator should preferably be a 5HT_{2B} receptor antagonist.

Preferred 5HT_{2B} receptor antagonist compounds expected to be useful in the above treatments include those of formula (IA) or pharmaceutically acceptable salts thereof:

10



(IA)

wherein:

- 15 P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R₁ is hydrogen or C₁₋₆ alkyl;

- 20 R₂, R₃, R₁₀ and R₁₁ are independently hydrogen or C₁₋₆ alkyl, or R₁₀ and R₁₁ together form a bond, or R₂ and R₁₀ or R₃ and R₁₁ together form a C₂₋₆ alkylene chain;

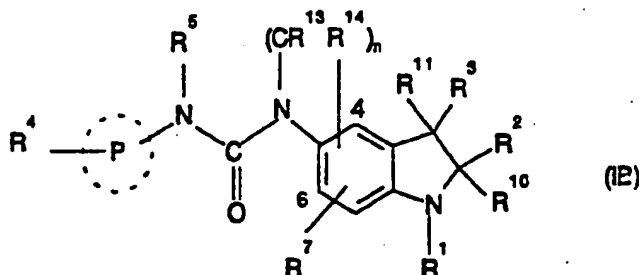
R₄ is hydrogen, C₁₋₆ alkyl, halogen, NR₈R₉, OR₁₂ or COOR₁₂, where R₈, R₉ and R₁₂ are independently hydrogen or C₁₋₆ alkyl;

R₅ and R₆ are independently hydrogen or C₁₋₆ alkyl; and

- 25 R₇ is hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen; and wherein the urea moiety is attached at the 4-, 5- or 6-position of the indole or indoline ring.

Preferred compounds of formula (IA) include those exemplified in WO 93/18028 and WO 92/05170, in particular N-(1-Methyl-5-indolyl)-N'-(3-methyl-5-isothiazolyl) urea. Compounds of formula (IA) can be prepared according to the procedures outlined in WO 93/18028 and WO 92/05170.

- 30 Further preferred 5HT_{2B} receptor antagonist compounds include those of formula (IB) or pharmaceutically acceptable salts thereof:



wherein:

P represents a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R¹ is hydrogen or C₁₋₆ alkyl;

R², R³, R¹⁰ and R¹¹ are independently hydrogen or C₁₋₆ alkyl, or R¹⁰ and R¹¹ together form a bond, or R² and R¹⁰ or R³ and R¹¹ together form a C₂₋₆ alkylene chain;

R⁴ is hydrogen, C₁₋₆ alkyl, halogen, NR⁸R⁹ or OR¹², where R⁸, R⁹ and R¹² are independently hydrogen or C₁₋₆ alkyl;

R⁵ is hydrogen or C₁₋₆ alkyl;

R⁷ is hydrogen, C₁₋₆ alkyl, OR¹² or halogen, where R¹² is hydrogen or C₁₋₆ alkyl; and n is 2 or 3; and

the groups R¹³ and R¹⁴ are independently hydrogen or C₁₋₆ alkyl.

Preferred compounds of formula (IB) include:

5-methyl-1-(3-pyridylcarbonyl)-2,3-dihydropyrrolo[2,3-f]indole,

6-methyl-3-(5-quinolylcarbonyl)-2,3-dihydro-pyrrolo[3,2-e]indole and

N-(5-isoquinolyl)-5-methyl-2,3-dihydropyrrolo[2,3-f] indole-1-carboxamide and pharmaceutically acceptable salts thereof.

Compounds of formula (IB) can be prepared according to the procedure outlined in PCT EP93/02031.

Certain compounds of formula (I), (IA) and (IB) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates.

Tautomers of compounds of formula (I), (IA) and (IB) and mixtures thereof will also exhibit 5HT_{2B} activity and therefore also form an aspect of the invention.

The compounds of the formula (I), (IA) and (IB) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

The present invention further provides a method of treatment or prophylaxis of CNS disorders such as epilepsy, migraine and feeding disorders, and GI disorders such as

IBS, which comprises administering to a host in need thereof an effective amount of a 5HT_{2B} receptor modulator or a pharmaceutically acceptable salt thereof.

In a still further aspect, the invention provides the use of a 5HT_{2B} receptor modulator or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of CNS disorders such as epilepsy, migraine and feeding disorders and GI disorders such as IBS.

Compounds which exhibit 5HT_{2B} receptor agonist and antagonist activity are also expected to be of use in the treatment and prophylaxis of other CNS disorders. Such disorders include anxiety, depression, obsessive compulsive disorders, pain, memory disorders such as Alzheimer's disease, sleep disorders, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

When used in therapy, the 5HT_{2B} receptor agonists and antagonists are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tableting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and

buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months.

Examples**1-(5-(2-thienylmethoxy)-1H-indol-3yl)-propan-2-amine****5 Description 1****5-Benzoyloxy-3-(2-trifluoroacetyl-amino)propylindole (D1)**

Trifluoroacetic anhydride (2.4 ml, 17 mmol) was added to a solution of 3-(2-aminopropyl)-5-benzoyloxyindole (prepared by the method of A.S.F. Ash and W.R. Wragg, *J. Chem. Soc.*, 1958, 3887; 4.65g, 16.6 mmol) and 4-(N,N-dimethylamino)pyridine (2.07g, 17 mmol) in dry dichloromethane (40 ml) at 0° C. The mixture was stirred for 1h at 0° C, then washed twice with water, dried and evaporated. The residue was chromatographed on silica gel eluted with 1-2% methanol/dichloromethane. Eluted product was recrystallised from dichloromethane/petrol to give the title compound (3.71g, 59%).

NMR (CDCl₃) δ : 1.23 (3H, d, J = 7), 2.46 (2H, m), 4.38 (1H, m), 5.11 (2H, s), 6.23 (1H, d, J = 7), 6.97 (2H, m), 7.13 (1H, d, J = 2), 7.30 (1H, d, J = 7), 7.38 (3H, m), 7.49 (2H, m), 8.03 (1H, s).

MS (EI) m/e 376 (M⁺)

Description 2**5-Hydroxy-3-(2-trifluoroacetyl-amino)propylindole (D2)**

Benzoyloxyindole (D1, 3.7g, 9.8 mmol) was shaken with 5% palladium on charcoal (0.47g) in ethanol (50 ml) under hydrogen at 50 p.s.i., for 43h. The mixture was filtered through kieselguhr and the filtrate was evaporated. The residue was chromatographed on silica gel eluted with 2% methanol/dichloromethane. Eluted product was recrystallised from dichloromethane/methanol to give the title compound (2.22g, 79%)

30

NMR (CDCl₃/CD₃OD) δ : 1.22 (3H, d, J = 7), 2.83 (1H, dd, J = 14,7), 3.00 (1H, dd, J = 14,5), 4.34 (1H, m), 6.82 (1H, dd, J = 7,2), 6.99 (1H, s), 7.08 (1H, d, J = 2), 7.22 (1H, d, J = 7), 8.28 (1H, s).

Description 3**5-(2-thienylmethoxy)-3-(2-trifluoroacetyl-amino)indole (D3)**

A solution of hydroxyindole (D2, 2.22g, 7.76 mmol) in dry dimethylformamide (15 ml) was added to a suspension of sodium hydride (80% in oil, 0.28g, 9.3 mmol) in dimethylformamide (15 ml) at 0° C. After 10 min at 0° C a solution of 2-chloromethylthiophene (1.06g, 8 mmol) in dimethylformamide (10 ml) was added and the mixture was heated for 2h at 90-110° C. The mixture was then evaporated and the residue was dissolved in dichloromethane and washed with dilute hydrochloride acid (pH3), sodium bicarbonate and water. The organic phase was dried and evaporated, and the residue was chromatographed on silica gel with 1-2% methanol/dichloromethane, to give the title compound (1.87g, 63%).

NMR (CDCl₃) δ: 1.26 (3H, d, J = 7), 2.98 (2H, m), 4.38 (1H, m), 5.28 (2H, s), 6.22 (1H, d, J = 7), 6.95 (1H, dd, J = 7,2), 7.00 (2H, m), 7.13 (1H, d, J = 4), 7.18 (1H, d, J = 2), 7.29 (1H, d, J = 7), 7.34 (1H, d, J = 6), 8.05 (1H, s).

MS (EI) m/e 382 (M⁺)

Example 1**1-[5-(2-Thienylmethoxy)-1H-indol-3-yl]propan-2-amine hydrochloride (E1)**

The trifluoroacetyl compound (D3, 1.86g, 4.87 mmol) was heated under reflux with potassium carbonate (3.82g, 27.7 mmol) in methanol (90 ml) and water (6 ml) for 6.5h. The mixture was partially evaporated and then partitioned between dichloromethane and water. The aqueous phase was further extracted with dichloromethane. Combined organic phases were washed with brine, dried and evaporated. The crude product (1.39g) was dissolved in ethyl acetate (50 ml) at 0° C and 1M hydrogen chloride/ether (4.9ml, 4.9 mmol) was added slowly. After stirring for 5 min at 0° C, the precipitate was filtered off, washed with ethyl acetate and dried, to give the title compound (1.40g, 89%), m.p. 203-205° C.

NMR (d₆-DMSO) δ: 1.19 (3H, d, J = 7), 2.80 (1H, dd, J = 14, 7), 3.09 (1H, dd, J = 14, 5), 5.31 (2H, s), 6.80 (1H, dd, J = 7,2), 7.03 (1H, dd, J = 6, 4), 7.20-7.31 (4H, m), 7.54 (1H, d, J = 6), 8.01 (1H, s).

MS (CI) m/e 287 (MH⁺)

Pharmacological Data

Epilepsy

5

5HT_{2B} receptor agonists are expected to be of use in the treatment of epilepsy since 1-(5-(2-thienylmethoxy)-1H-indol-3-yl)propan-2-amine (1-100 mgkg⁻¹ s.c. 30 min pretest) significantly raised the current at which 50% of mice convulsed in the mouse maximal electroshock seizure (MES) threshold test, carried out as described in Loscher and Schmidt, (1988, *Epilepsy Res.*, 2, 145-181). This is consistent with the presence of 5HT_{2B} receptor mRNA in the rat hippocampus, an area which can mediate convulsions (McNamara et al., 1993, in *Epilepsy, models, mechanisms and concepts*, Ed, Schwartzkroin, Cambridge University Press, pp 27-47).

10

15 IBS

5HT_{2B} receptors are expressed in the stomach fundus of the rat (Foguet et al., 1992, *EMBO J.*, 11, 3481-3487) where they mediate a contractile response to 5-hydroxytryptamine (5-HT). 1-(5-(2-thienylmethoxy)-1H-indol-3-yl)propan-2-amine also causes contraction of rat stomach fundus and is a selective agonist at 5HT_{2B} receptors in this preparation (pEC₅₀[95% Confidence limits] = 8.47 [8.04 - 8.90]).

20

In bilaterally vagotomised spinal rats, 1-(5-(2-thienylmethoxy)-1H-indol-3-yl)propan-2-amine (1-100 µgkg⁻¹ i.v.) evokes a dose-dependant and significant increase in gastric motility in vivo causing a significant increase in intragastric pressure (for methodology see Dhasmana et al., 1992, *Eur. J. Pharmacol.*, 213, 293-299). This action is blocked by selective 5HT_{2B} receptor antagonists such as those disclosed in Patent (WO 93/18028) and supports a use for 5HT_{2B} receptor modulators in disorders of gastric motility. Such a use is further supported by the observation that the 5HT_{2B} receptor antagonist 6-methyl-3-(5-quinolinylcarbamoyl)-2,3-dihydro-pyrrolo[3,2-e]indole (10 - 10000 µgkg⁻¹ s.c.) significantly reduced 5-hydroxytryptophan-induced increase in faecal pellet output in the conscious mouse (for methods see Banner et al., 1993, *Br. J. Pharmacol.*, 110, 17P).

25

30

Feeding Disorders

35

When given at doses between 1 and 100 mgkg⁻¹ s.c. 30 min pretest, or at doses between 1 and 30 µg i.c.v. 4 min pretest, 1-(5-(2-thienylmethoxy)-1H-indol-3-yl)propan-2-amine

significantly increases feeding behaviour and food intake in freely-feeding, sated rats. The methodology used in these studies was as described in Kennett et al., (1992, Eur. J. Pharmacol., 141, 429-435). Thus 5HT_{2B} receptor agonists are expected to be of therapeutic use in the treatment of feeding disorders such as anorexia nervosa and bulimia.

- 5 Furthermore, selective 5HT_{2B} receptor antagonists are likely to have appetite suppressant actions and be beneficial in the treatment of obesity. These claims are supported by the presence of high levels of 5HT_{2B} receptor mRNA in the hypothalamus (studies carried out at SmithKline Beecham Pharmaceuticals), an area long associated with the control of appetite (Sugrue et al., 1987, Neuropharmacology, 32, 145-182).

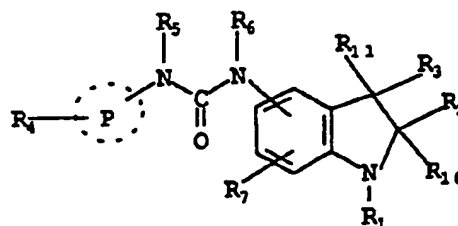
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Migraine

- 1- (5-(2-thienylmethoxy)-1H-indol-3-yl)-propan-2-amine (mean pEC₅₀ [95% C.L.] 7.9 [7.7 - 8.1] with an intrinsic activity (IA) of 0.84 ± 0.04, n=9) and 5-HT (mean pEC₅₀ [95% C.L.] 8.2 [8.0 - 8.3] IA 1.0, n=9) evokes endothelium-dependant relaxation of isolated rat jugular vein via activation of 5HT_{2B} receptors with a maximal relaxation to 5HT of 73.8 ± 4.6%, n=9 (for basic methods see Bodelsson et al., 1993, J. Pharm. Exp. Ther., 264, 709 - 716). Endothelium-dependant 5HT-induced relaxation of isolated smooth muscle preparations has been suggested to be due to release of endothelium derived nitric oxide (Martin et al., 1992, Br. J. Pharmacol., 105, 643 - 652). Local application of 5HT to cerebral arterioles in vivo induces dilatation which is antagonised by inhibitors of nitric oxide synthase (Parsons et al., 1992, In: 5-Hydroxytryptamine mechanisms in primary headaches, Ed. Olesen & Saxena, Raven Press, NY, pp157 - 162) suggesting the presence of cerebrovascular 5HT_{2B} receptors. Furthermore the pharmacological character of the receptor mediating the dilation is that expected for 5HT_{2B}. Agonist potency order α-methyl 5HT = 5HT > 5CT. (Pryke et al., Brit. J. Pharmacol. 1989, 98, 685p). Dilatation of cerebral arteries has been shown to induce a migraine-like headache (Nichols et al., 1991, Stroke, 21, 555 - 559). 5HT_{2B} receptor modulators are therefore expected to be effective in the treatment or prophylaxis of migraine.

CLAIMS:

1. Use of a 5HT_{2B} receptor antagonist for the treatment of migraine.
2. Use according to claim 1 in which the 5HT_{2B} receptor antagonist is a
- 5 compound of formula (IA) or a pharmaceutically acceptable salt thereof:



(IA)

10

wherein:

P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

15 R₁ is hydrogen or C₁₋₆ alkyl;

R₂, R₃, R₁₀ and R₁₁ are independently hydrogen or C₁₋₆ alkyl, or R₁₀ and R₁₁ together form a bond, or R₂ and R₁₀ or R₃ and R₁₁ together form a C₂₋₆ alkylene chain;

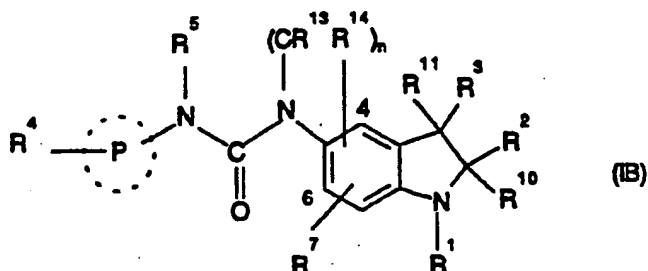
R₄ is hydrogen, C₁₋₆ alkyl, halogen, NR₈R₉, OR₁₂ or COOR₁₂, where R₈, R₉ and R₁₂ are independently hydrogen or C₁₋₆ alkyl;

20 R₅ and R₆ are independently hydrogen or C₁₋₆ alkyl; and

R₇ is hydrogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or halogen; and wherein the urea moiety is attached at the 4-, 5- or 6-position of the indole or indoline ring.

3. Use according to claim 1 in which the 5HT_{2B} receptor antagonist is a compound of formula (IB) or a pharmaceutically acceptable salt thereof:

25



(IB)

wherein:

P represents a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic

heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R^1 is hydrogen or C_{1-6} alkyl;

R^2, R^3, R^{10} and R^{11} are independently hydrogen or C_{1-6} alkyl, or R^{10} and R^{11} together form a bond, or R^2 and R^{10} or R^3 and R^{11} together form a C_{2-6} alkylene chain;

R^4 is hydrogen, C_{1-6} alkyl, halogen, NR^8R^9 or OR^{12} , where R^8, R^9 and R^{12} are independently hydrogen or C_{1-6} alkyl;

R^5 is hydrogen or C_{1-6} alkyl;

R^7 is hydrogen, C_{1-6} alkyl, OR^{12} or halogen, where R^{12} is hydrogen or C_{1-6} alkyl; and

n is 2 or 3; and

the groups R^{13} and R^{14} are independently hydrogen or C_{1-6} alkyl.

4. Use according to claim 3 in which the compound of formula (IB) is

5-methyl-1-(3-pyridylcarbamoyl)-2,3-dihydropyrrolo[2,3-f]indole,

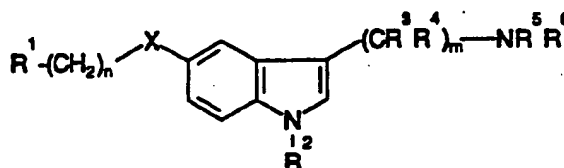
6-methyl-3-(5-quinolinylcarbamoyl)-2,3-dihydro-pyrrolo[3,2-e]indole, or

N-(5-isoquinolyl)-5-methyl-2,3-dihydropyrrolo[2,3-f] indole-1-carboxamide or pharmaceutically acceptable salts thereof.

5. Use of a $5HT_{2B}$ receptor agonist in the treatment of epilepsy and feeding disorders.

6. Use according to claim 5 in which the $5HT_{2B}$ receptor agonist is a

compound of formula (I) and pharmaceutically acceptable salts thereof:



(I)

in which

R^1 is an optionally substituted phenyl, thienyl or furyl ring;

R^2 is hydrogen or C_{1-6} alkyl;

R^3 and R^4 are independently hydrogen or C_{1-6} alkyl;

R^5 and R^6 are independently hydrogen or C_{1-6} alkyl;

X is O, S or NH; and

n and m are independently 1 or 2.

7. Use according to claim 6 in which the $5HT_{2B}$ receptor agonist is 1-(5-(2-thienylmethoxy)-1H-indol-3-yl)propan-2-amine or a pharmaceutically acceptable salt thereof.